REMARKS

Continued prosecution and consideration of the claimed subject matter in the accompanying patent application is respectfully requested.

Claims 26, 41, 46, 54 and 58 have been amended and claims 57 and 59 cancelled. Claims 26, 31-32, 34, 36-41, 46, 52-56, 58 and 60-61 are in the case and are before the Examiner. Claims 42-45 and 47-51 were previously withdrawn.

I. The Amendments

Independent claims 26, 41, 46, 54 and 58 have been amended to more clearly define the invention and to speed prosecution. More specifically, those claims have been amended to recite that the antigen part of the fusion protein "consists essentially of an immunogenic extracellular part of an M2 membrane protein of a human influenza A virus", or a similar phrase, and thereby more clearly recites that only an external part of the M2 protein is used as antigen. This amendment is supported by the claims as previously written and discussed through out the application. Certain of the claims have also been amended to tighten and the claim language and to make it more consistent among the claims.

Claims 57 and 59 have cancelled as being redundant.

These amendments add no new matter.

II. The Action

A. Rejections Under 35 USC §103

1. First Rejection

Claims 26, 31, 32, 36, 38, 41, 46, 53-55 and 58-61 were rejected as allegedly obvious from the combined teachings of Pumpens et al, *Intervirology*, 1995 **38**:63-74 (Pumpens) and Slepushkin et al., *Vaccine*, 1995 **13(15)**:1399-1402 (Slepushkin). Briefly, Pumpens teaches that HBcAg or HBc particles are good epitope carriers and can accommodate epitopic sequences at the N-, or C-terminus as well as within the sequence. Slepushkin is said to teach that the full length M2 protein is highly conserved and could function as a subunit vaccine to protect mice upon expression in a baculovirus membrane preparation to protect mice from challenge, but could not protect mice from challenge when expressed as part of a vaccinia recombinant.

The Action again asserts that the Slepushkin disclosure provides the motivation for modifying its M2 with the HBc carrier of Pumpens, because that paper teaches that "others have failed to find any protective effect against challenge with influenza virus following vaccination of mice or ferrets with a vaccinia-M2 recombinant", and now augments that argument by saying that the success of Slepushkin "is not the only way to increase the immunogenicity ofM2 available in the art."

It is again submitted that the "motivation" of Slepushkin is inadequate. In particular, Slepushkin demonstrates protection from influenza by his M2 composition, thereby overcoming the problems of the prior art to which he refers. Consequently, there existed no apparent motivation to *further* modify the M2 composition of Slepushkin. On the other hand, if the Action's position were correct, then every success

reported would be motivation to go further. It is submitted that such is not the law.

It is again noted that a key distinction between the combination of Pumpens and Slepushkin and the claimed invention is that the proposed combination would suggest the use of the full-length M2 (as did Slepushkin, see page 1399, col. 2, paragraph 2), whereas the claimed construct employs an *extracellular* part of M2 (*i.e.*, "M2e"). The Action asserts that the previously utilized language could include the full length M2 protein. It is submitted that the present amendments clarify the point that only an external portion of that protein is used as an antigen for which use there is no teaching from either relied-on paper that suggests that one should use anything except the longer, full length sequence.

The Action asserts now that the external portion of the M2 protein would be a logical choice as it is more exposed to the immune system. This basis cannot be agreed with because a viral antigenic protein is processed into shorter polypeptides by cells of the immune system, and the resulting polypeptides are then presented on cell surfaces by the MHC class of proteins. The proteins destined for such presentation can be derived from any portion of the engulfed viral protein, and not just from external portion of such proteins. As a consequence, upon infection with influenza virus, one would expect peptides from all over the M2 protein sequence to be presented on the cell surfaces to constitute targets for the immune system. This point is particularly shown in Table 2 of Slepushkin wherein the strongest antibody response was generated to an intracellular epitope of M2, PM8. One would therefore not consider the external portion of M2 to be a good candidate for an antigen.

It is again noted that the positive results of Slepushkin were obtained with the full length protein. Again, Slepushkin failed to provide any indication for the role of serum antibodies in immunoprotection by passive transfer of the sera *in vitro* and, above all, *in vivo*. If as the Action contends, the extracellular M2 part were the antigen of choice, one would have expected serum antibodies would bind to that portion and provide protection. That is not what is taught in the article, and as such, the assertion recited in the Action that use of the external M2 portion would be "more valuable" is incorrect and should be withdrawn as should this basis for rejection.

2. Second Rejection

Claim 37, "wherein the fusion product [of the immunogenic composition of claim 26] is anchored in the membrane of an acceptor cell expressing the fusion product" has been again been rejected over the combined teachings of Pumpens and Slepushkin as above further in view of Highfield et al., AU-B-49273/90. The Highfield disclosure is used to support the assertion that a skilled worker could express "a fusion construct from any acceptable cell line." This basis for rejection cannot be agreed with for several reasons and is respectfully traversed.

First, as noted above, the combination of Pumpens and Slepushkin does not lead one of ordinary skill to the subject matter of claim 26 and therefore the addition of the Highfield disclosures that add nothing regarding the deficiencies of those teachings cannot make dependent claim 37 obvious. Thus, this basis for rejection should be withdrawn.

Second, even if the combination of the Pumpens and Slepushkin teachings were to lead a skilled worker to the subject matter of claim 26, and even if Highfield teaches that a skilled worker could express "a fusion construct from any acceptable cell line", neither of which is believed to be the case, it is submitted that a teaching of expression in "any acceptable cell line" is quite different from expression that leads to "the fusion product [of claim 26 being] anchored in the membrane of an acceptor cell expressing the fusion product" as is claimed.

The present Action has clarified its position that because M2 is a membrane protein, one would expect that upon fusion to a carrier, the resulting fusion protein would also be anchored in a membrane. It is first submitted that the present amendments clarify that only an extracellular portion of the M2 protein is used. That being the case, and based on the logic expressed in the Action, if the whole protein were membrane-bound and the portion used here sticks out, away from the membrane into the fluids, one would expect the claimed fusion protein to not be membrane-bound, but to be secreted as its antigen portion is normally found in fluid, not a membrane. Contrary to that expectation, the fusion protein is membrane-bound and as such, this basis for rejection should be withdrawn.

c. Third Rejection

Claims 34 and 39 were rejected as allegedly obvious from the combined teachings of Pumpens and Slepushkin as in the first rejection and Highfield in the second rejection further in view of van de Guchte et al., *Appl. Environm. Microbiol.* 1989 **55(1):**224-228 (van de Guchte). The van de Guchte disclosure teaches lactococcal expression vectors that can express a wide

range of heterologous genes. This basis for rejection cannot be agreed with and is respectfully traversed.

The arguments provided above in response to the Second Rejection are repeated here by reference. As such, it is submitted that there is no expectation of success in regard to the recited and above quoted subject matter regarding expression of the immunogenic materials in or on the Lactococci cell walls. It is thus submitted that this basis for rejection should also be withdrawn

d. Fourth Rejection

Claims 40 and 53 that depend from claim 26 have been rejected over the combined teachings of Pumpens and Slepushkin as discussed above, further in view of Kedar et al., US Patent No. 5,919,480 (Kedar). The Kedar patent is said to disclose the influenza hemagglutinin and neuraminidase proteins in combination with a cytokine as a vaccine. The Action asserts that it would be obvious to add known vaccine antigens and an immunostimulating cytokine in influenza immunogenic composition of claim 26. This basis for rejection cannot be agreed with and is respectfully traversed.

The previously-made arguments concerning the inapplicability of the combination of the Pumpens and Slepushkin teachings to suggestion of the immunogenic composition of claim 26 are hereby repeated here. It is apparent that with no mention being made of a carrier such as HBc, a fusion protein or the M2 protein, the Kedar patent has no disclosures that could overcome the deficits already noted in the Pumpens and Slepushkin teachings regarding the claimed subject matter. Inasmuch as the subject matter claimed in claims 40 and 52 is dependent upon claim 26, and because that independent claim is

not obvious from the basic Pumpens and Slepushkin teachings, the dependent claim cannot be obvious from a teaching that does not augment the first two disclosures. This basis for rejection should therefore be withdrawn.

e. Fifth Rejection

Claims 26, 31, 32, 36, 38, 41, 46, 53, 54, and 57-61 were rejected as allegedly obvious from the teachings of Pumpens and Slepushkin as discussed before further in view of Sunstrom et al., *J. Membrane Biol.*, 1996 **150**:127-132 (Sundstrom) or Hongo et al., *J. Virol.*, April 1997 **71(4)**:2786-2792 (Hongo). The Sunstrom teaching is cited for its disclosure that influenza B NB protein forms an ion channel, whereas Hongo is said to teach that influenza C virus CM2 protein has similar properties to the M2 protein. The Action's logic is that because the NB and CM2 proteins are similar in function to M2, it would be obvious to use either or both in place of M2 in a Pumpens construct. This basis for rejection cannot be agreed with and is respectfully traversed.

First, the previous discussion of the inadequacies of the combination of Pumpens and Slepushkin are repeated here by reference. As such alone, this basis for rejection should be withdrawn.

In addition, use of the NB and CM2 proteins as antigens is no longer claimed to speed prosecution of this application. It is thus believed that this basis for rejection is moot and should be withdrawn.

III. Summary

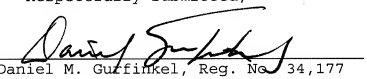
Independent claims 26, 41, 46, 54 and 58 have been amended and claims 57 and 59 cancelled. Each basis for rejection or objection has been overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution. It is noted that the present application is now subject to large entity fees. Those fees are enclosed.

Respectfully submitted,

By 
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Enclosures
Petition for Extension of Time and fee
RCE and fee

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